MAJOR ARTICLE

Prevalence of Genital Human Papillomavirus Among Females in the United States, the National Health and Nutrition Examination Survey, 2003–2006

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Background. Genital human papillomaviruses (HPV) include >40 sexually transmitted viruses. Most HPV infections do not progress to disease, but infection with certain types of HPV can cause cervical and other anogenital and oropharyngeal cancer, and other types of HPV are associated with anogenital warts. HPV vaccines prevent infection with HPV 16 and 18, which account for 70% of cases of cervical cancer, and HPV 6 and 11, which cause 90% of the cases of anogenital warts.

Methods. Using data and self-collected cervicovaginal specimens from 4150 females, 14–59 years of age, from consecutive National Health and Nutrition Examination Surveys (2003–2006), we estimated the prevalence of type-specific HPV DNA and examined sociodemographic and sexual determinants.

Results. The overall prevalence of HPV was 42.5% in females 14–59 years of age and varied significantly by age, race or ethnicity, and number of sex partners. Individual type prevalence was less than 7%, ranging from <0.5% through 6.5%. The most common type was nononcogenic HPV 62 (found in 6.5% of subjects), followed by HPV 53 and HPV 16 (4.7%), both of which are oncogenic types. The most prevalent species was nononcogenic α3.

Conclusions. HPV infection is common among US females, with the highest burden of infection found in young females 20–24 years of age. Monitoring trends in HPV type distribution will contribute to our understanding of the early impact of HPV vaccines.

Genital human papillomaviruses (HPV) include >40 closely related but genetically distinct sexually transmitted viruses that are usually classified as high-risk (HR) or low-risk (LR) according to their oncogenic potential [1–3]. HPV infections are common, and the majority of infections do not lead to disease. Notably, there are different levels of disease risk associated with specific HPV types, and persistent infection with certain oncogenic types is a strong predictor of HPV-related cancers. Therefore, the distribution of HPV types in the general population does not reflect the prevalence of HR types in individuals with HPV-associated cancers. However, strong epidemiologic evidence indicates that infection with certain HR HPV types is necessary for the development of virtually all cervical cancers, a high proportion of other anogenital cancers, and a subset of oral cavity and oropharyngeal cancers [4–6]. Of these, HPV 16 and 18 alone are responsible for >70% of all cases of cervical cancer [4]. LR HPV types, including HPV 6 and 11, are causally related to ∼90% of anogenital warts and essentially all cases of recurrent respiratory papillomatosis [7]. Since 2006, a quadrivalent

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vaccine against HPV types 6, 11, 16, and 18 has been recommended in the United States for routine use in 11- or 12-year-old females with catch-up through 26 years of age for the prevention of cervical cancer and anogenital warts [8]. In October 2009, a bivalent vaccine against HPV types 16 and 18 was licensed for routine use in females 9–26 years of age. Either vaccine is now recommended for use in females [9]. Also in October 2009, the quadrivalent vaccine received US Food and Drug Administration approval for prevention of genital warts in males aged 9–26 years [10].

Understanding the epidemiology of HPV infection at the population level prior to vaccine introduction can be useful for monitoring early vaccine-related changes in HPV type distribution. The first nationally representative estimate of HPV infection in US females using data from the 2003–2004 National Health and Nutrition Examination Survey (NHANES) was published in 2007 [11]. This analysis updates national estimates of type-specific HPV infection as detected by the Linear Array (LA) genotyping assay among females 14–59 years of age using 4 years of NHANES data from the period 2003–2006. Additionally, we describe the prevalence of HPV infection by oncogenic risk category and by species group, and we explore the influence of demographic characteristics and sexual behavior on the prevalence of HPV infection.

METHODS

Survey Design and Population

NHANES is an ongoing series of cross-sectional surveys conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC). The surveys are designed to be nationally representative of the civilian, noninstitutionalized US population. Consenting participants have a household interview followed by a physical examination in a mobile examination center (MEC). Some groups, such as adolescents, African Americans, and Mexican Americans, are oversampled in NHANES to allow sufficient sizes for subgroup analysis. This study was approved by the NCHS Research Ethics Review Board.

We assembled NHANES data from 2003–2006 for this analysis. The combined unweighted household interview response rate for that period was 79.9% ($n = 20{,}470/25{,}623$); the examination response rate was 76.5% ($n = 19{,}593/25{,}623$). From 2003 through 2006, 5178 females 14–59 years of age were interviewed; 4990 (96.4%) received an examination in the MEC. All females 14–59 years of age who attended the MEC were asked to self-collect a cervicovaginal swab sample. Of those individuals, 4233 (85%) submitted swab samples, 83 of which were inadequate for DNA typing. Combining the 2003–2006 data was justified, because there was no significant difference in HPV prevalence between 2003–2004 and 2005–2006 as detected by the LA assay (results not shown).

Demographic and Behavioral Data

Demographic information, including age, race, education, marital status, and country of birth, was ascertained from all participants during the household interviews. Poverty index was calculated according to the US Census definition by dividing total family income by the poverty threshold after adjusting for family size at the time of the interview.

Sexual history information was self-reported by participants aged 14–59 years using an audio computer-assisted self-interview. Respondents who reported ever having sex (described as vaginal, oral, or anal) were asked additional questions about their sexual history, including questions regarding the number of sex partners and sexual orientation.

Specimen Collection and Processing

Female participants 14–59 years of age who had an examination in the MEC were asked to self-collect a cervicovaginal swab sample. As described previously [11], each participant was given a collection device, which was a small foam swab on a plastic handle packaged in an individual reclosable plastic sleeve (Catch-All Sample Collection Swabs; Epicentre). Participants took swabs and instructions into a bathroom and collected the samples in privacy. Swabs were given to NHANES personnel, stored at room temperature, and mailed within 1 week to the CDC laboratory, where they were kept at 4°C and extracted within 1 month of collection.

Laboratory Methods

DNA Isolation. Extractions were performed within 1 month of sample collection using modified QIAmp Mini Kit (Qiagen) as previously described [11]. The extract (100 µL total volume) was tested immediately or stored at –20°C. For every 40 samples, a water blank was processed through all steps of extraction to serve as a contamination control.

HPV Genotyping Test (Linear Array Assay). HPV detection and typing were performed on all specimens from 2003–2006 using the Research Use Only LA genotyping assay (Roche Diagnostics). This assay uses HPV L1 consensus polymerase chain reaction (PCR) with biotinylated PGMY09/11 primer sets and β-globin as an internal control for sample amplification. The manufacturer's protocol was modified to use 5 µL extract in the 100-µL PCR reaction but was otherwise unchanged. All samples were hybridized to the typing strip that included probes for 37 HPV types (6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, XR(52), 53, 54, 55, 56, 58, 59, 61, 62, 64, 66, 67, 68, 69, 70, 71, 72, 73, 81, 82, 83, 84, 89, and IS39). Samples that were positive for the XR probe on the LA HPV strip that were also positive for HPV 33, 35, and 58 required further evaluation to confirm or exclude the presence of HPV 52. An HPV 52 quantitative PCR assay using an ABI 7900 HT Sequence Detection System (Applied Biosystems) with type-specific primers and a FAM-labeled TaqMan probe, together with β-globin–specific primers and probe with a threshold of 50 copies, was used to determine the

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status of HPV 52 in these [12]. Samples negative for both β-globin and HPV (n = 83) were considered to be inadequate for interpretation and were omitted from further analysis.

Statistical Analysis

Analysis was restricted to female respondents aged 14–59 years whose self-collected cervicovaginal swab samples were adequate for DNA typing (n = 4150). Data were analyzed using SAS, version 9.1 (SAS Institute) and SAS-callable SUDAAN (RTI International). Variance estimates were calculated using a Taylor series linearization to account for the complex cluster survey design [13]. All estimates were weighted using 4-year weights constructed from the MEC examination weights provided by NCHS to account for the unequal probabilities of selection and adjustment for nonresponse. The weighting methodology has been described previously [14]. Confidence intervals (CIs) were calculated using a logit transformation with the standard error of the logit prevalence based on the delta method and applying SUDAAN estimated standard errors [15].

We estimated the overall prevalence of infection with any HPV type by sociodemographic and sexual behavior characteristics. We further evaluated the prevalence of HR and LR HPV infection separately by the same characteristics and examined the prevalence of individual HPV types within each risk category stratified by age group.

Risk categories were determined on the basis of oncogenic risk and phylogenetic relatedness to oncogenic HPV types. The LR category included HPV 6, 11, 55, 40, 42, 54, 71, 61, 62, 72, 81, 83, 84, and 89; the HR category included HPV 16, 31, 33, 35, 52, 58, 67, 64, 73, 18, 39, 45, 59, 68, 70, 26, 51, 69, 82, IS39, 53, 56, and 66. Because species classification has been suggested to be predictive of carcinogenicity, we also examined HPV infection within phylogenetically related species groups in each risk category [1, 2, 15]. The species and associated HPV types evaluated included α5 (HPV 26, 51, 69, 82, and IS39), α6 (HPV 53, 56, and 66), α7 (HPV 18, 39, 45, 59, 68, and 70), α9 (HPV 16, 31, 33, 35, 52, 58, and 67), α11 (HPV 64 and 73), α3 (HPV 61, 62, 72, 81, 83, 84, and 89), α10 (HPV 6, 11, and 55), α13 (HPV 54), α1 (HPV 42), α8 (HPV 40), and α15 (HPV 71).

We used a Wald χ^2 test to evaluate bivariate associations between HPV prevalence and selected characteristics. Weighted percentages and 95% CIs are presented. Prevalence estimates with a relative standard error (RSE) ≥30% were considered to be unstable and are indicated. No adjustments for multiple comparisons were made for P values.

An unconditional logistic regression model was used to explore the relationship between HPV infection and sexual behaviors and other risk factors. Any variable with a Wald χ^2 P value of <.1 was included in the logistic regression model. Associations were considered significant if the P value for the Satterthwaite adjusted F test was <.05, and those variables were retained in the main effects model. Confounding was assessed to ensure that no parameter estimate of significant variables changed by ≥30%. All pairwise interactions in the final model were examined and were considered to be significant if the P value for the Satterthwaite adjusted F test was <.05.

RESULTS

Overall HPV Prevalence

Overall prevalence of any HPV type as measured by HPV DNA positivity by the LA assay was 42.5% (95% CI, 40.3%–44.7%) among 14–59-year-old US females (Table 1). Using 2003–2006 census estimates, this represents 39.5 million (95% CI, 37.4–41.5 million) noninstitutionalized females aged 14–59 years in the United States with prevalent HPV infection [17].

Prevalence of any HPV infection was lowest among 14–19-year-old females (32.9%), increased to 53.8% (P < .001) among 20–24-year-old females, and decreased to 38.8% in 50–59-year-old females (P = .002). In bivariate analysis, non-Hispanic blacks had the highest overall prevalence (59.2%) followed by Mexican Americans (44.2%) and non-Hispanic whites (39.2%). HPV prevalence was significantly higher among those below the poverty level (56.5%), compared with those at or above the poverty level (39.7%), and was significantly associated with several measures of sexual activity, including the number of lifetime sex partners, number of sex partners within the past year, age at sexual debut, and marital status. HPV prevalence was also significantly higher in those with a history of diagnosed genital warts. There were no significant differences in HPV prevalence by country of birth, current use of oral contraceptives, hysterectomy (data not shown), or ever having sex with a woman. HPV prevalence was 15% among females who reported never having sex and significantly increased with increasing age: 9.8% in 14–19-year-old females, 12% in 20–39-year-old females, and 47.1% among 40–59-year-old females (P = .001).

Variables that were significant in bivariate analysis were further evaluated in a logistic regression model. Marital status and number of sex partners within the past year were independent predictors of HPV infection in the model. After adjusting for other variables, HPV DNA was more likely to be detected in females with ≥3 sex partners within the past year, compared with females who had a single sex partner within the past year (adjusted odds ratio [aOR], 2.0; 95% CI, 1.2–3.3) and in those who had never married but were living with a partner versus those who were currently married (aOR, 3.3; 95% CI, 2.4–4.6). We also found a statistically significant interaction between race and the number of lifetime sex partners. Figure 1 illustrates the relationship between the 2 factors as indicated by prevalence and suggests that the number of lifetime sex partners is associated with HPV infection in all race groups except non-Hispanic blacks.

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Table 1. Weighted Prevalence of Human Papillomavirus (HPV) Among Female Respondents 14–59 Years of Age by Demographic and Sexual Behavior Characteristics, National Health and Nutrition Examination Survey, 2003–2006

		Any HPV	Low-risk HPV (with or without high-risk HPV)	High-risk HPV (with or without low-risk HPV)
Variables	Sample size	Prevalence (95% CI)	Prevalence (95% CI)	Prevalence (95% CI)
Total	4150	42.5 (40.3–44.7)	28.5 (26.8–30.3)	29.0 (26.8–31.3)
Age, years		*	*	*
14–19	1363	32.9 (29.5–36.5)	22.2 (19.2–25.5)	25.3 (22.0–28.8)
20–24	432	53.8 (45.9–61.5)	35.5 (29.5–41.9)	43.4 (36.0–51.2)
25–29	403	46.8 (42.9–50.8)	34.1 (29.9–38.5)	30.8 (25.8–36.2)
30–39	702	44.2 (40.5–48.0)	29.6 (25.6–34.0)	30.4 (26.8–34.3)
40–49	705	42.4 (39.0–46.0)	27.9 (24.8–31.3)	27.3 (23.8–31.1)
50–59	545	38.8 (33.9–44.0)	25.7 (21.3–30.5)	23.5 (19.1–28.6)
Race/ethnicity		*	*	*
Non-Hispanic white	1705	39.2 (37.0–41.4)	26.1 (24.0–28.2)	26.9 (24.7–29.1)
Non-Hispanic black	1134	59.2 (55.7–62.6)	41.5 (38.8–44.4)	39.6 (34.9–44.6)
Mexican American	991	44.2 (38.6–50.1)	28.6 (23.7–34.1)	30.7 (25.2–36.9)
Other	320	41.8 (34.4–49.5)	27.7 (22.5–33.7)	28.2 (21.2–36.5)
Education[a]		**	*	*
Less than high school	797	54.0 (48.6–59.3)	37.1 (32.5–42.0)	38.2 (33.3–43.4)
High school graduate	806	46.6 (42.8–50.4)	32.6 (28.7–36.8)	33.2 (30.2–36.3)
More than high school	1682	40.7 (37.7–43.7)	26.4 (24.3–28.6)	26.8 (24.1–29.6)
Marital status[a]		*	*	*
Married	1507	33.3 (30.9–35.9)	21.3 (19.4–23.5)	21.2 (18.7–24.0)
Widowed/divorced/separated	469	57.9 (51.5–64.1)	42.5 (37.2–48.0)	36.9 (30.3–44.0)
Never married	1005	52.9 (47.9–57.9)	34.2 (29.9–38.7)	40.7 (36.3–45.2)
Living with Partner	304	65.5 (59.3–71.2)	45.8 (37.8–54.0)	46.6 (39.1–53.9)
Poverty level		**	*	*
Below	1004	56.5 (51.0–61.9)	39.2 (33.7–45.0)	39.7 (34.9–44.6)
At or above	2962	39.7 (37.5–41.9)	26.4 (24.6–28.2)	26.8 (24.6–29.1)
Country of birth				
United States	3374	42.8 (40.6–45.1)	28.9 (27.0–30.9)	29.4 (27.1–31.7)
Mexico	475	40.5 (33.7–47.6)	24.9 (19.8–30.9)	27.6 (21.4–34.8)
Other	301	40.6 (32.4–49.3)	26.6 (19.8–34.9)	26.5 (20.1–34.1)
Age at sexual debut		*	*	*
<16 Years	1073	55.8 (51.2–60.3)	38.8 (34.5–43.3)	39.2 (35.0–43.6)
≥16 Years	2089	40.6 (37.7–43.6)	26.9 (24.7–29.3)	27.2 (24.6–30.0)
Never had sex	656	15.0 (10.9–20.1)	9.6 (6.5–14.0)	8.7 (5.7–13.2)
Total lifetime sex partners		*	*	*
0	656	15.0 (10.9–20.1)	9.6 (6.5–14.0)	8.7 (5.7–13.2)
1	709	18.2 (14.2–23.0)	10.9 (8.5–14.0)	11.2 (8.2–15.3)
2	385	37.8 (31.7–44.3)	22.4 (17.7–28.0)	24.6 (18.7–31.5)
3–5	902	48.1 (44.7–51.5)	32.6 (28.7–36.6)	32.3 (28.9–35.8)
≥6	1141	55.9 (52.6–59.1)	38.8 (35.9–41.8)	39.4 (35.8–43.2)
Total sex partners within past 12 months[a]		*	*	*
0	308	39.7 (34.1–45.6)	26.6 (21.7–32.3)	24.0 (18.6–30.4)
1	2007	40.7 (37.9–43.5)	26.4 (24.4–28.5)	27.1 (24.4–30.1)
2	240	60.2 (51.0–68.9)	42.3 (32.6–52.7)	49.4 (41.9–56.9)
≥3	224	76.2 (66.7–83.7)	58.7 (49.3–67.4)	54.1 (47.2–60.8)
Same sex partner[a]				
Yes	205	51.1 (42.7–59.3)	37.7 (29.6–46.5)	33.5 (26.2–41.7)
No	2587	43.9 (41.3–46.5)	29.2 (27.0–31.5)	30.0 (27.5–32.6)
History of genital warts diagnosis[a]		*	*	*
Yes	168	62.1 (53.4–70.0)	45.8 (36.0–56.0)	42.6 (33.8–51.8)
No	2637	43.1 (40.8–45.5)	28.6 (26.5–30.8)	29.3 (27.1–31.6)

NOTE. CI, confidence interval.

[a] 18–59 Years old.

* $P < .005$ by Wald χ^2.

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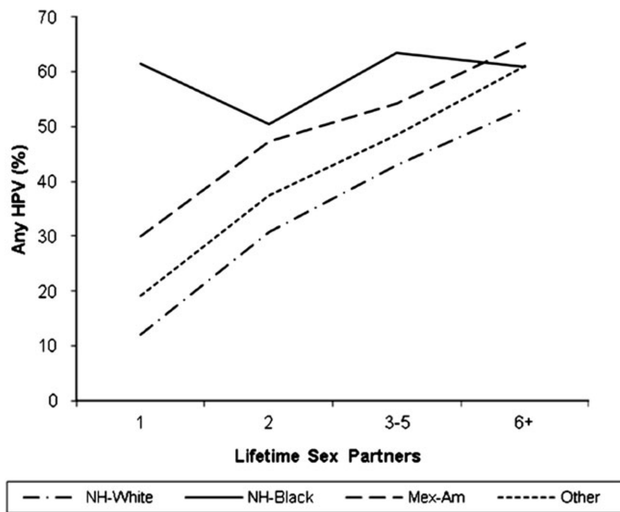

Figure 1. Weighted prevalence of any human papillomavirus (HPV) among female respondents 18–59 years of age by number of lifetime sex partners and race category. Mex-Am, Mexican American; NH, non-Hispanic.

HPV Type and Species Prevalence by Oncogenic Risk Category

Among females 14–59 years of age, the prevalence of any of the 23 HR types was 29.0% (95% CI, 26.8%–31.3%); prevalence of any of the 14 LR types was 28.5% (95% CI, 26.8%–31.3%) (Table 1). The prevalence of any HR and LR types was similar across all covariates examined, including age group (Figure 2). Type-specific prevalence ranged from <0.5% to 6.5% overall; the range of type-specific prevalence was similar in both risk categories (Figure 3). The 5 most prevalent LR types were HPV 62 (6.5%), HPV 84 (4.8%), HPV 89 (4.6%), HPV 83 (4.1%), and HPV 61 (4.0%). Among HR types, HPV 53 (5.8%) was the most common, followed by HPV 16 (4.7%), HPV 51 (4.1%), HPV 52 (3.6%), and HPV 66 (3.6%).

The 23 LR HPV types evaluated in this analysis were represented by 6 species groups, whereas the 14 HR HPV types were distributed across 5 species groups. The $\alpha3$ species group included half (7 of 14) of all LR types and accounted for over half

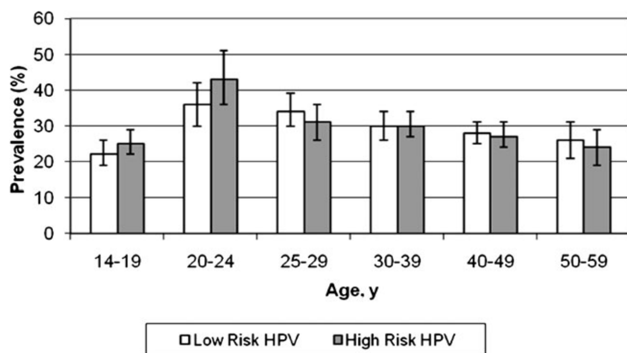

Figure 2. Weighted prevalence of low-risk and high-risk human papillomavirus (HPV) among female respondents 14–59 years of age, by age group.

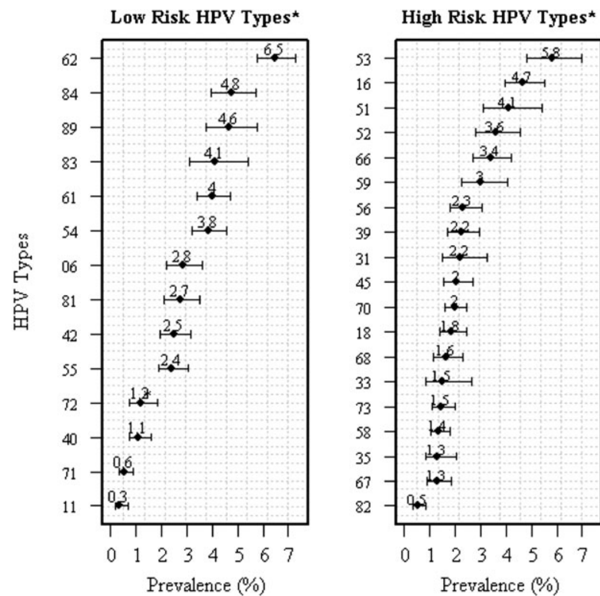

Figure 3. Type-specific human papillomavirus (HPV) prevalence among female respondents 14–59 years of age. *HPV types 69, 64, 26, and IS39 have a relative standard error ≥30% and are not presented in the figure above.

(75.5%) of all cases of LR HPV infection. The prevalence of $\alpha9$ species group, which includes HPV 16, was 13.2% (95% CI, 11.6%–15.1%), whereas the prevalence of $\alpha7$ species, which includes HPV 18, was 11.3% (95% CI, 9.9%–12.8%) (Figure 4). Combined, the $\alpha9$ and $\alpha7$ species groups represented the majority of HR HPV infections (71.9%) among those with any HR HPV infection.

DISCUSSION

We found a high overall prevalence of HPV (42.5%) in US females 14–59 years of age. Estimates from the current study are higher than previously reported for NHANES 2003–2004 data [11] because of a change in the laboratory methods used to detect HPV DNA [18]. The previous study reported an overall HPV prevalence of 26.8% (95% CI, 23.3%–30.9%) based on the Roche line-blot prototype assay, which was provided as analyte-specific reagents and was discontinued with the availability of the standardized commercial LA kit. When the same specimens were retested with the LA assay, HPV prevalence increased to 45.1% (95% CI, 42.1%–48.0%) overall and by 70%–100% across various sociodemographic and sexual behavior groups. The higher positivity is thought to be attributable to detection of very low levels of HPV DNA rather than to analytic false-positive results [19]. Small differences in assay sensitivity may be magnified in samples with some compromise in DNA quality, such as from the dry vaginal swabs, and in populations with low levels of HPV DNA [18]. However, the possibility of lower analytic specificity, although not likely, cannot be ruled out. Given the

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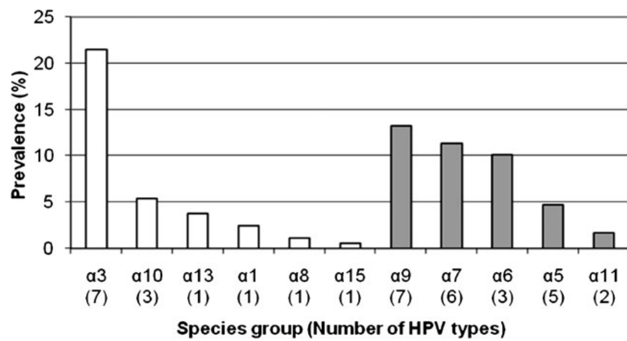

Figure 4. Weighted human papillomavirus (HPV) prevalence among female respondents 14–59 years of age, by species group. Shaded bars indicate species groups that include oncogenic HPV types, and unshaded bars indicate species groups that include non-oncogenic HPV types. α9 species includes vaccine type 16, α7 species includes vaccine type 18, and α10 species includes vaccine types 6 and 11.

rapid evolution of HPV DNA–based technology and the development of more accurate and more valid tests for detection of HPV DNA, our results underscore the importance of standardized testing procedures and test validation over time.

Consistent with other data, we found that the prevalence of any HPV significantly increased after 14–19 years of age, peaking in young women 20–24 years of age. The observed age distribution in this study supports the body of epidemiologic evidence that suggests that first HPV infection is acquired shortly after a woman becomes sexually active [20–22]. We also found that HPV prevalence continued to gradually but significantly decrease through 59 years of age. Age-related reductions in HPV prevalence are likely attributable to a variety of factors, including clearance over time, decreased incidence as a result of changes in sexual activity, and acquired immunity from previous infection.

Our results suggest that the effect of the number of lifetime sex partners on HPV detection differs by race. Specifically, although the prevalence of HPV was proportional to the number of lifetime sex partners in non-Hispanic whites and Mexican Americans, the prevalence in non-Hispanic blacks was high even with 1 lifetime partner and did not significantly increase with increasing numbers of lifetime sex partners. The reasons for this racial disparity are not clear, but it may be explained by differences in the prevalence of HPV infection or in the structure of race-specific sexual networks that may confer increased risk of HPV transmission with a single partner in non-Hispanic blacks compared with other race categories. Of note, the interaction between race and the number of sex partners has been observed with other sexually transmitted infections (STIs). For example, data from NHANES indicate that, among respondents reporting only 1 lifetime sex partner, HSV-2 seroprevalence is significantly higher in non-Hispanic blacks than in whites, suggesting a higher prevalence of other STIs within black communities [23].

Although sexual activity, as determined by various metrics, was independently associated with HPV detection, 15.0% of respondents who reported never having sex also had HPV detected. This finding could be attributable to multiple factors, including misclassification of self-reported behavior. For example, HPV has been detected in persons with only external genital contact [24]. Some NHANES participants who had only had external genital contact with 1 or more sexual partners may have not considered themselves sexually experienced, whereas others may not have been comfortable answering sexual behavior questions. Unweighted analysis of this group suggested self-report bias in at least 24% of these respondents who reported being either married, divorced, or living with a partner and in 11% of respondents who tested positive for HSV-2. Of note, the overall HPV prevalence in those who reported that they never had sex was 36.5% among non-Hispanic blacks (95% CI, 27.1%–47.1%) and 9.6% among non-Hispanic whites (95% CI, 6.0%–15.0%). When removing those who reported that they were married, widowed, divorced, or living with a partner or who were positive for another STI, the rate of HPV DNA detection was lower: 18.3% (95% CI, 9.9%–31.2%) among non-Hispanic blacks and 8.1% (95% CI, 4.4%–14.3%) among non-Hispanic whites. Nonsexual transmission of HPV in these respondents is also possible [25].

We found that, among LR HPV types, a single species group, α3, represented the majority of HPV detected, including the 5 most prevalent types. HPV types in this species group are detected more frequently in vaginal specimens according to other studies [26–28]. This has led to the postulation that certain phylogenetically related types may preferentially infect and/or persist in vaginal tissue, compared with cervical tissue. Our results may overrepresent the vaginal milieu, because NHANES specimens were self-collected cervicovaginal swab samples [28]. However, given the high correlation between self-collected and clinician-collected specimens for HR types, any differences attributable to specimen collection method may be limited to certain LR types, such as those in the α3 species [28, 29].

In our study, the prevalence of HR HPV was 29.0%. It is important to note, however, that HPV risk classification is evolving as more information becomes available on the natural history of infection. In our classification, we included HPV types that are phylogenetically related to known oncogenic types, but for which there is limited evidence of cervical cancer in humans [30]. The primary reason for selecting this classification was to enable comparison with the earlier NHANES analysis. However, emerging opinion is to restrict classification to oncogenic types with strong epidemiologic evidence of being associated with disease in humans [31]. This approach would exclude HPV 53, which is the most prevalent type (5.8%); HPV66 (3.4%); and other less frequent α6 species types, thereby decreasing HR prevalence by up to ~10% in this analysis. When we restricted the analysis to only types that are detected by current clinical HPV tests (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68), the overall prevalence was 23.7% (95% CI, 21.6%–

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26.0%). Of note, the HR HPV tests licensed for clinical use are designed to detect DNA for any of only 13 or 14 HR HPV types, rather than the 23 types included in the LA assay. Moreover, these tests are used for clinical management of cervical disease and thus have different performance characteristics than those of the LA assay. The analytic threshold of clinically approved HPV DNA assays would result in fewer positive samples than were found in the current analysis. It should also be noted that NHANES participants represent the general population, including females with normal cytological characteristics as well as females with various stages of cervical abnormality. Thus, our results are not directly comparable to estimates of HPV prevalence from other international studies that are based on select populations of females with normal cytological characteristics.

This study has some limitations. First, the data are cross-sectional in nature and cannot distinguish incident from prevalent infection. Moreover, the evaluations are based on HPV DNA testing which, although it is the best indicator of current infection, is not a measure of cumulative exposure, because HPV DNA may clear or become undetectable in previously infected individuals. Therefore, the prevalence estimates do not reflect lifetime risk of HPV infection. Serologic testing provides a better estimate of cumulative infection [32], but it can also underestimate past infection because not all naturally infected individuals develop an antibody response. Second, as mentioned above, the self-collected swab specimens used for this study contain a mixture of vaginal and cervical cells. Finally, self-reported information on risk factors and other characteristics examined are subject to misclassification.

Recent data from vaccine trials suggest that both vaccines may provide partial efficacy against phylogenetically related HR types [33, 34]. Therefore, a reduction of nonvaccine types proportional to the protective effects of vaccine on these types may occur in the general population. On the other hand, a reduction in vaccine-type HPV infection may open a niche for nonvaccine types to increasingly cause infection and associated disease [35–37]. This phenomenon has been observed with other vaccine-preventable diseases but is considered unlikely for HPV [38]. Continued monitoring of HPV infection through NHANES will be an important strategy for evaluating early population impact of current and future HPV vaccines and may be useful for guiding policy and public health practice [39].

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